REMARKS

The Office Action of August 30, 2002 has been received and reviewed. Claims 1-31 are currently pending in the application. Claims 23, 25 and 26 have been withdrawn from consideration as assertedly being drawn to a non-elected invention and claims 1-22, 24 and 27-31 stand rejected. Claims 1-15, 18-19, 21, 22, 24 and 29-31 have been amended and claims 33-39 have been added as set forth herein. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Priority Claim

Submitted herewith is a copy of priority document PCT/NL99/00509.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-22, 24 and 27-31 were rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. At least partially in view of the amendments to the claims, applicants respectfully traverse the rejections.

Specifically, it was thought that the phrases "epitope being broken under specifically chosen different conditions" and "lie within physiologically acceptable limits" of claim 1 were unclear and indefinite. Although applicants do not agree that the phrases are indefinite, for the sake of expedited prosecution, the claims have been amended to recite "first conditions" in place of "specifically chosen conditions" and "second conditions" in place of "specifically chosen different conditions." The amendments clarify that the "first conditions" refer to the "specifically chosen conditions" and the "second conditions" refer to the "specifically chosen different conditions."

With regard to the phrase "lie within physiologically acceptable limits," it has been amended to recite "lie within physiologically acceptable limits of a human or an animal body." When read in conjunction with the specification, the phrase has a definite meaning. (*See*, Specification, page 3, lines 20-26).

In view of the amendments and remarks presented herein, applicants respectfully request reconsideration and withdrawal of the indefiniteness rejections of claims 1-22, 24 and 27-31.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-22, 24 and 27-31 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly not providing enablement for an antibody or fragment thereof which binds to an epitope and is broken from an epitope under broadly recited conditions. At least partially in view of the amendments to the claims, applicants respectfully traverse the rejections.

Specifically, it was thought that the specification was only enabling for an antibody, or fragment thereof, which binds to an epitope and is broken from an epitope under the conditions listed in Table 1.

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. (M.P.E.P. § 2164.01(b), *citing In re Fischer*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)). The specification discloses a method for obtaining an antibody, or fragment thereof, that binds to an epitope under first conditions and where the bond between the antibody, or fragment thereof, is broken from the epitope under second conditions, wherein the first and second conditions lie within physiologically acceptable limits of a human or an animal body.

For instance, as disclosed in the specification, Example 1 describes the selection of antibodies, or fragments thereof, that recognize a specific epitope using a Fab-phage library as the starting point. (*See*, Specification, page 6, lines 5-9). Further, positive clones were shown to bind specifically to the epitope, *e.g.*, the bacteria, at the first, or specifically chosen, conditions. (*See*, *Id.* at page 9, lines 10-15). Some of the positive clones that bound to the epitope under the first conditions, *e.g.*, the binding buffer, were shown to elute from the epitope under second conditions, *e.g.*, the elution buffer. (*See*, *Id.* at page 9, lines 15-25). Further, the binding and elution conditions, *i.e.*, the first and second conditions, respectively, are within

physiological acceptable limits of a human or an animal body as defined in the specification. (*See*, *Id.* at Table 1 and page 3, lines 20-26).

As long as the disclosure contains sufficient information regarding the subject matter of the claims to make and use the claimed invention without undue experimentation, the claims are enabled. (*See*, M.P.E.P. § 2164.01). Since one of skill in the art would be able to isolate an antibody, or fragment thereof, that binds an epitope under one set of conditions, such as a binding buffer, from a library and select the antibody, or fragment thereof, that elutes from the epitope under a second set of specifically chosen conditions, such as an elution buffer, using the teachings of the present invention without undue experimentation, the claims are enabled. Further, one of skill in the art would be able to determine or select both sets of conditions such that they lie within physiologically acceptable limits.

With further regard to claims 4-8, 10 and 12, it was asserted that since overlapping ranges of pH (claims 4-8) and ion strength (claims 10 and 12) were recited, that it was unknown how mutually exclusive endpoints can be achieved at the same pH and ion strength. Although applicants do no agree that the claims are not enabled, for the sake of expedited prosecution the claims have been amended.

Amended claim 4 recites in part "wherein the physiologically acceptable limits are a pH of between about 4 and about 8.5." As amended, claim 4 clarifies that the first conditions are a pH between about 4 and about 8.5 and the second conditions are at a different pH between about 4 and about 8.5.

With regard to the overlapping of ranges in claims 5-8 and 12, the claims have been amended to clarify that the pH or ion concentration is within one range or another range. For instance, claim 5 recites in part "the first conditions are at a pH within a range of between about 4 and about 7 or another range of between about 7 and about 8.5; and the second conditions are at a pH of about 7." As amended, the pH of the first conditions is a pH within the range of between about 4 and about 7 or another range of between about 7 and about 8.5, while the second conditions are a pH of about 7. Claims 6-8 and 12 have been amended in a similar manner to clarify that the first conditions and the second conditions do not occur at multiple pHs or ion concentrations, but that the pH or ion concentration is selected from different ranges.

In view of the amendments and remarks presented herein, applicants respectfully request reconsideration and withdrawal of the enablement rejections of claims 1-22, 24 and 27-31.

Rejections under 35 U.S.C. § 102

Claims 1-4, 6-22 and 28-31 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Beggs et al. (U.S. Patent 5,490,988) as evidenced by Goding (Monoclonal Antibodies; Principles and Practice, 1983, Academic. Press, New York). Applicants respectfully traverse the rejections as hereinafter set forth.

The Office Action indicated that Beggs et al. teaches an antibody, or fragment thereof, that is able to bind a target site. (Office Action, page 5). The Office Action further stated that although Beggs et al. does not explicitly state that bonds between the antibody, or fragment thereof, and antigen can be broken under specifically chosen conditions, that as evidenced by Goding, it is considered to be an inherent property of all antibodies, or fragments thereof, that the binding of the antibody to the epitope is reversible and depends on pH and ionic strength. (*Id.*).

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. Inherency, however, may not be established by probabilities or possibilities.'" (M.P.E.P. § 2112, *quoting In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949 (Fed. Cir. 1999)). As further stated by the Federal Circuit "[t]o serve as anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such [extrinsic] evidence must make clear that the missing descriptive is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991).

The extrinsic reference, Goding, states that "[m]onoclonal antibodies may behave quite differently ... in some cases, it may be possible to alter antigen or antibody quite extensively without destruction of binding. In others, it may be found that seemingly minor modifications to antibody or antigen may abolish binding completely ... some monoclonal antibodies may be very susceptible to minor changes." (Goding, page 44).

Goding indicates that, generally, monoclonal antibodies possess varying characteristics and behave differently, but does not specifically mention the antibodies of Beggs et al. Thus, the extrinsic evidence does not make clear that the bond between the antibody and the epitope of Beggs et al. is broken under second conditions that lie within physiologically acceptable limits. Further, since Goding does not specifically refer to the antibodies of Beggs et al., the limitation of "the bond of the antibody, or fragment thereof, to the epitope is broken under second conditions" missing from Beggs et al. is not necessarily present in Goding as required to establish inherency. Lastly, since Goding was published in 1986 (*See, Id.* at Title Page) and Beggs et al. was not filed until 1990 (*See*, Beggs et al., Foreign Application Priority Date), at the earliest, it stands to reason that Goding cannot be used to show what was necessarily present in Beggs et al.

Therefore, since Beggs et al. does not expressly or inherently disclose all of the limitations of claim 1, claim 1 is not anticipated.

Claims 1-4, 6-21, 24, 27, 28 and 30-31 also stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Cummins et al. (EP 0736544) as evidenced by Goding. Applicants respectfully traverse the rejections as hereinafter set forth.

As previously established herein, Goding indicates that, generally, monoclonal antibodies possess varying characteristics and behave differently. Since Goding does not specifically mention the antibodies of Cummins et al. and Goding was published in 1986 before Cummins et al. (*See*, Cummings et al., Date of Filing 1995), the descriptive matter missing in Cummins et al. is not necessarily present in Goding as required to establish inherency.

Therefore, since Cummins et al. does not expressly or inherently disclose all of the limitations of the claim 1, claim 1 is not anticipated.

Applicants respectfully request reconsideration and withdrawal of the anticipation rejections of claim 1, and claims 2-4, 6-22 and 28-31 depending therefrom.

Rejections under 35 U.S.C. § 103

Claims 1-22 and 28-31 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Beggs et al. or Cummins et al. in view of Goding. Applicants respectfully traverse the rejections as hereinafter set forth.

A *prima facie* case of obviousness cannot be established since the cited references do not teach or suggest all of the claim limitations of independent claim 1. Neither Beggs et al. nor Cummins et al., alone or in combination with Goding, teach or suggest an antibody, or fragment thereof, which binds an epitope under first conditions and where the bond of the antibody, or fragment thereof, to the epitope is broken under second conditions, wherein the first and second conditions lie within physiologically acceptable limits of a human or an animal body.

The Office Action asserted that "Goding teaches that during optimization of each purification protocol for each antibody of interest and a fragment thereof, the parameters such as pH and ionic strength play an essential role and that it is an inherent propert[y] of all antibody and fragment to bind an epitope under one set of specifically chosen conditions and be eluted from an epitope (bound of antibody to an epitope is broken) under specifically chosen different conditions." (Office Action, page 8). The Office Action further stated "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to determine all operable and optimal ranges of pH and ion strength at which antibody or fragment thereof binds to and eluted from an epitope." (*Id.*).

However, as previously discussed herein with regard to the anticipation rejections, Beggs et al. and Cummins et al. merely disclose an antibody binding to an epitope. Beggs et al. and Cummins et al. do not teach or suggest the bond between the antibody and the epitope being broken under second conditions that lie within physiological limits. In fact, Beggs et al. and Cummins et al. do not disclose the bond being broken at all. Further, Goding does not teach or suggest an antibody, or fragment thereof, which binds an epitope under first conditions and where the bond of the antibody, or fragment thereof, to the epitope is broken under second conditions, wherein the first and second conditions lie within physiologically acceptable limits of a human or an animal body. Rather, Goding merely discloses, generally, that monoclonal antibodies possess varying characteristics and behave differently.

Therefore, all of the claim limitations of independent claim 1 are not taught or suggested by the cited references as required to establish a *prima facie* case of obviousness. Dependent claims 2-22 and 28-31 are nonobvious, at the very least, as depending from nonobvious independent claim 1. (*See, In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)).

Claim 29 stands rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Beggs et al. in view of Goding as applied to claims 1-22 and 28-31, and further in view of Cole et al. (Immunol. & Infect. Diseases, 1993, 3, 33-35). Applicants respectfully traverse the rejections as hereinafter set forth.

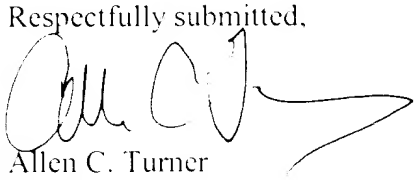
Claim 29 is nonobvious, at the very least, as depending from nonobvious independent claim 1. (*See, In re Fine, supra*).

In view of the amendments and remarks presented herein, applicants respectfully request reconsideration and withdrawal of the obviousness rejections of claims 1-22 and 28-31.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully submit that the claims define patentable subject matter. If any questions remain after consideration of the foregoing, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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MARKED UP VERSION OF CLAIMS SHOWING CHANGES MADE

1. (Amended) An antibody, or fragment thereof, [which] wherein:

the antibody, or fragment thereof, binds to an epitope under [specifically chosen] first conditions[,];

the bond of the antibody, or fragment thereof, to the epitope [being] is broken under [specifically chosen different] second conditions[,];

wherein both the [specifically chosen binding] first conditions and the second conditions [under which the bond is broken] lie within physiologically acceptable limits of a human or an animal body.

2. (Twice amended) The antibody, or fragment thereof, of claim 1 [characterized in that] wherein the antibody, or fragment thereof, [binds to] is coupled to a diagnostically, therapeutically or cosmetically active substance.

3. (Twice amended) The antibody, or fragment thereof, of claim 1, [characterized in that] wherein the [specifically chosen binding] first conditions and the second conditions [under which the bond is broken] are dependent upon pH.

4. (Amended) The antibody, or fragment thereof, of claim 3, [characterized in that the antibody, or fragment thereof, binds to the epitope at a pH within a range of 4 and 8.5, and the bond between the antibody, or fragment thereof, and the epitope is broken at a different pH within the range of 4 and 8.5] wherein the physiologically acceptable limits are a pH of between about 4 and about 8.5.

5. (Amended) The antibody, or fragment thereof, of claim 3, [characterized in that] wherein:

the [antibody, or fragment thereof, binds to the epitope] first conditions are at a pH within a range [chosen from a range] of between about 4 and about 7 [and a] or another range of between about 7 and about 8.5[,]; and

the [bond between the antibody, or fragment thereof, and the epitope is broken] second conditions are at a pH of about 7.

6. (Amended) The antibody, or fragment thereof, of claim 3, [characterized in that] wherein:

the [antibody, or fragment thereof, binds to the epitope] first conditions are at a pH of about 7[,]; and

the [bond between the antibody, or fragment thereof, and the epitope is broken] second conditions are at a pH within a range [chosen from a range] of between about 4 and about 7 [and a] or another range of between about 7 and about 8.5.

7. (Amended) The antibody, or fragment thereof, of claim 3, [characterized in that] wherein:

the [antibody, or fragment thereof, binds to the epitope] first conditions are at a pH within a range [chosen from a range] of between about 4 and about 6 [and a] or another range of between about 8 and about 8.5[,]; and

the [bond between the antibody, or fragment thereof, and the epitope is broken] second conditions are at a pH of between about 6 and about 8.

8. (Amended) The antibody, or fragment thereof, of claim [2] 3, [characterized in that] wherein:

the [antibody, or fragment thereof, binds to the epitope] first conditions are at a pH of between about 6 and about 8[,]; and

the [bond between the antibody, or fragment thereof, and the epitope is broken] second conditions are at a pH within a range [chosen from a range] of between about 4 and about 6 [and a] or another range of between about 8 and about 8.5.

9. (Twice amended) The antibody, or fragment thereof, of claim 1, [characterized in that] wherein the [specifically chosen binding] first conditions and the second conditions [under which the bond is broken] are dependent upon ion strength or pH.

10. (Amended) The antibody, or fragment thereof, of claim 9, [characterized in that] wherein:

the [antibody, or fragment thereof, binds to the epitope at an] first conditions are a first ion strength within a range of between about 0 M and about 13 M[,]; and

the [bond between the antibody, or fragment thereof, and the epitope is broken at a] second conditions are a second [different] ion strength within the range of between about 0 M and about 13 M.

11. (Amended) The antibody, or fragment thereof, of claim 9, [characterized in that] wherein:

the [antibody, or fragment thereof, binds to the epitope] first conditions are at an ion strength within a range of between about 0 mM and about 500 mM[,]; and

the [bond between the antibody, or fragment thereof, and the epitope is broken] second conditions are at an ion strength within [the] a range of between about 1 M and about 13 M.

12. (Amended) The antibody, or fragment thereof, of claim 9, [characterized in that] wherein:

the [antibody, or fragment thereof, binds the epitope at] first conditions are a first pH within a range of between about 4 and about 8.5, [and/or at an] a first ion [concentration] strength within a range of between about 0 M and about 13 M, or a combination thereof[,]; and

the [bond between the antibody, or fragment thereof, and the epitope is broken at] second conditions are a [different] second pH within the range of between about 4 and about 8.5, [and/or] a [different] second ion strength within the range of between about 0 M and about 13 M, or a combination thereof.

13. (Twice amended) The antibody, or fragment thereof, of claim 1, [characterized in that] wherein the antibody, or fragment thereof, [comprises] is selected from a group consisting of a F(ab), F(ab)', $F(ab)'_2$ [or] and an scFv.

30. (Twice amended) A composition comprising:
at least one antibody, or fragment thereof, [as claimed in] of claim 1; and
at least one physiologically acceptable [dilutent] diluent, solvent or carrier.

31. (Twice amended) [A] The composition [useful as] of claim 30, wherein the composition is selected from the group consisting of a teeth cleaning agent, mouthwash, mouth spray, chewing tablet, chewing gum, cream [or] and ointment [comprising:
at least one antibody, or fragment thereof, as claimed in claim 1; and
at least one physiologically acceptable diluent].

14. (Twice amended) The antibody, or fragment thereof, of claim 1, wherein said antibody, or fragment thereof, is capable of use in a targeted or temporary diagnostic, therapeutic and cosmetic treatment of externally accessible parts of [a] the human or [an] the animal body.

15. (Amended) The antibody, or fragment thereof, of claim 14, wherein said targeted or temporary diagnostic, therapeutic or cosmetic treatment comprises a treatment of an oral cavity of [a] the human or [an] the animal body.

18. (Amended) The antibody, or fragment thereof, of claim 15, wherein said antibody, or fragment thereof, is capable of removing plaque in said oral cavity.

19. (Amended) The antibody, or fragment thereof, of claim 14, wherein said targeted or temporary diagnostic, therapeutic or cosmetic treatment comprises a treatment for fighting infections in externally accessible parts of [a] the human or [an] the animal body.

21. (Amended) The antibody, or fragment thereof, of claim 20, wherein the enzyme is [chosen] selected from [a] the group consisting of an oxidase, a peroxidase, a protease, a cell-wall lysing enzyme and a plaque matrix inhibitor.

22. (Amended) The antibody, or fragment thereof, of claim 21, wherein the enzyme comprises an oxidase [chosen] selected from [a] the group consisting of glucose oxidase, lactase oxidase and uric acid oxidase.

24. (Amended) The antibody, or fragment thereof, of claim 21, wherein the enzyme comprises [a] the protease [chosen] and is selected from [a] the group consisting of papain, pepsin, trypsin, ficin and bromelin.

29. (Amended) The antibody, or fragment thereof, of claim 28, wherein said pathogenic micro-organism is [chosen] selected from [a] the group consisting of Actinomyces actinomycetem comitans, Porphyromonas gingivalis, Prevotella intermedia, Streptococcus mutans, Bacteroides forsythus, Eikenella corrodens, Treponema denticola, Campylobacter lectus, and Fusobacterium nucleatum.